II. Rejections Under 35 U.S.C. §102

In the Office Action mailed June 19, the Examiner stated that the prior art rejection under 35 U.S.C. §102(b) is "maintained for the reasons of record." Claims 1-61 were previously rejected under 35 U.S.C. §102 as anticipated by U.S. Patent No. 4,943,590, to Boegesoe and U.S. Patent No. 4,136,193 to Boegesoe, in the final Office Action dated October 19, 2001.

During a telephone conference with the undersigned on September 20, 2002, Supervisory Examiner Alan Rotman indicated that the anticipation rejection would be withdrawn, in view of the amendments and arguments in the amendment mailed April 19, 2002, and the accompanying Declaration of Hans Petersen.

It is respectfully requested that the anticipation rejection now be withdrawn.

III. Rejections Under 35 U.S.C. §103

In the Office Action mailed June 19, the Examiner stated that the obviousness rejection under 35 U.S.C. §103 is "maintained for the reasons of record." In the Final Office Action dated October 19, 2001, claims 1-61 were rejected under 35 U.S.C. §103 as obvious over U.S. Patent No. 6,147,072, to Bymaster. During a telephone conference with the undersigned on September 20, 2002, Supervisory Examiner Alan Rotman indicated that the obviousness rejection would be reconsidered in view of arguments and evidence of unexpected results.

The Examiner is now requested to reconsider the obviousness rejection, in view of the following remarks.

Applicants respond separately to the method of crystallization claims, the crystal claims, the tablet claims and the method of manufacturing tablets claims.

A. Method of Crystallization Claims

The invention of claims 20-33 and 46-58 is directed to novel methods of crystallizing a pharmaceutically acceptable salt of the pharmaceutically active ingredient citalopram, wherein the median particle size of the crystals is at least 40 μm.

Applicants maintain that the method of crystallization claims are not obvious because none of the cited references describe or suggest the claimed method steps. Claim 20 calls for forming a solution of a pharmaceutically acceptable salt of citalopram in a solvent system at a first temperature, cooling the solution to a second temperature, seeding the solution by addition of crystals of the citalopram salt, followed by holding the solution at the second temperature and a controlled cooling the solution down to a third temperature, and isolating the crystals. The remaining method of crystallization claims 21-33 and 46-58 are dependent from claim 20.

The claimed method of crystallization is nowhere described or suggested in Bymaster (which is silent on crystallization), or in any of the other references of record, including U.S. Patent Nos. 4,943,590, 4,136,193, and 4,650,884.

As stated at paragraphs 4 and 5 of the Declaration of Hans Petersen, the '193 patent does not describe a method of crystallizing a salt of citalopram. Crystallization methods are described in the Examples of the '884 and '590 patents.

In Example 2 of the '884 patent, beginning at col. 5, l. 39, crystals of citalopram hydrobromide are dissolved in a methanol/2-propanol solvent and cooled. The resulting material is dissolved in solvent, cooled, and seeded with crystals, and the resulting crystals are washed. The method of the '884 patent does not teach or suggest the claimed controlled cooling of the solution to a third temperature, as required by claim 20.

In Example 3 of the '590 patent, beginning at col. 7, l. 14, citalopram base was dissolved in a methanol/2-propanol solvent to form the hydrobromide salt, and the mixture was left overnight. The method of the '590 patent does not recite the method of claim 20, including the controlled cooling step.

In addition, the claimed methods of crystallization result in citalopram salt crystals having a significantly larger median particle size than crystals formed from prior art methods (see specification at page 3, lines 18-21 and 30-32). The median particle size of the crystals is unexpected in view of the prior art.

In view of the arguments made, it is believed that the above referenced obviousness rejections of method of crystallization claims 20-33 and 46-58 has been overcome, and it is respectfully requested that the rejection be withdrawn.

B. Crystal Claims

The invention of claims 16-19, 44 and 45 cover crystals of a pharmaceutically acceptable salt of citalopram, wherein the median particle size of the citalopram salt crystals is at least 40 μm.

The claimed crystals have a significantly larger median particle size than citalopram salt crystals known in the prior art (see specification at page 3, lines 18-21 and 30-32), and demonstrate a significant improvement in flowability over prior art citalopram salt crystals. As explained in the specification at page 2, lines 10-16, the median particle size of crystals is an important factor in flowability. Crystals having a larger median particle size (comparable to the size of fillers) generally have good flowability, while particles having a smaller median particle size (around 2-20 μm) have poor flowability.

Crystals having good flowability, such as crystals having a median particle size of greater than 40 μm, demonstrate significant advantages in the manufacture of tablets (page 2, lines 4-7). For example, tablets comprising an active ingredient with good flowability may be prepared by direct compression (page 2, lines 5-7), which is a preferred method of forming tablets (page 3, lines 11-13). Particles having poor flowability, such as crystals having a median particle size of less than 20 μm, typically segregate or demix during direct compression tabletting (page 2, lines 12-22). In order to form acceptable tablets, crystals having the smaller median particle size require the more energy intensive operations performed in wet granulation or melt granulation tablet manufacture.

As explained in the Declaration of Hans Petersen, at paragraph 14, all known prior art methods of crystallizing citalopram and salts thereof, such as the methods disclosed in U.S. Patents Nos. 4,943,590 and 4,650,884, result in crystals having a median particle size of less than 20 μm [1]. Thus, citalopram salt crystals having good flowability were unknown in the prior art. There was no teaching or suggestion in the prior art that larger size salt crystals of citalopram having a median particle size of greater than 40 μm could be formed.

In view of the arguments made, it is believed that the above referenced obviousness rejection of crystal claims 16-19, 44 and 45 has been overcome, and it is respectfully requested that the rejection be withdrawn.

C. Tablet Claims

Claims 1, 4-10, 12, 13, and 36-43 cover tablets formed by direct compression comprising a pharmaceutically acceptable salt of citalopram, wherein the median particle size of the crystals is greater than 40 μm.

As explained above, all prior art crystals of citalopram salts had a median particle size of less than 20 μm. As a result, one of ordinary skill in the art would expect from the prior

[1] The Examiner has acknowledged the difference in particle size over the prior art. In the Office Action mailed June 19, 2002, the Examiner stated as follows:

> The examiner agrees with the applicants arguments that the cited prior art references (patents 590 and 884) do not mention the median particle size of the crystals and furthermore, the applicants have submitted a declaration ... showing that the particle size of crystals of citalopram was much smaller in the patents 590 and 884 (6-14 μm) as compared to at least 40 μm in the instant application.

art that tablets of a pharmaceutically acceptable salt of citalopram formed by direct compression would demonstrate segregation or de-mixing.

The crystallization methods disclosed and claimed in this application unexpectedly result in citalopram salt crystals having a median particle size of greater than 40 μm. This discovery led to advantages in the manufacture of pharmaceutical tablets, *e.g.* the ability to form stable pharmaceutical tablets comprising citalopram (or a salt thereof) by direct compression. The Examiner is referred to the specification at Example 6, at pages 12-13. This example describes use of the large size crystals of the method of the invention to form a tablet by direct compression. As stated at page 13, line 28, the tablets had satisfactory technical properties.

According to the Court of Appeals for the Federal Circuit, "[o]ne way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of 'unexpected results,' *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 34 U.S.P.Q.2d 1684, 1687 (Fed. Cir. 1995). The court also stated as follows:

> The basic principle behind this rule is straightforward -- that which would have been surprising to a person or ordinary skill in the relevant art would have not been obvious. The principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results. *Id.*

The evidence of record, both from the Declaration of Hans Petersen and from the specification as filed, establishes that the claimed tablets are unexpected to one of ordinary skill, in view of the prior art. Hence, the claimed tablets are non-obvious over the cited art.

In view of the arguments made, it is believed that the above referenced obviousness rejection of tablet claims 1, 4-10, 12, 13 and 36-43 has been overcome, and it is respectfully requested that the rejection be withdrawn.

D. Method of Manufacturing Tablet Claims

Claim 59 calls for providing a solution of a pharmaceutically acceptable salt of citalopram in a solvent at a first temperature, cooling the solution to a second temperature below the first temperature; seeding the solution with crystals of the citalopram salt; holding the solution at the second temperature for a predetermined period of time; cooling the solution to a third temperature that is lower than the second temperature to form citalopram crystals having a median particle size of at least 40μm; isolating the crystals from the solution; and directly compressing a predetermined quantity of crystals into a tablet.

The crystallization step of "cooling the solution to a third temperature that is lower than the second temperature to form crystals having a median particle size of at least 40μm" is neither described nor suggested in the cited art. Consequently, the prior art did not contemplate tablets formed from crystals of a pharmaceutically acceptable salt of citalopram with a median particle size of greater than 40 μm. As a result, the claimed methods of manufacturing tablets are not obvious over the cited art.

In view of the arguments made, it is believed that the above referenced obviousness rejection of method of manufacturing tablet claims 59 and 61 has been overcome, and it is respectfully requested that the rejection be withdrawn.

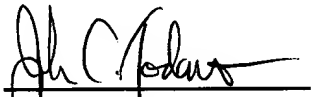
III. Conclusion

In view of the foregoing, it is believed that all pending claims 1, 4-10, 12, 13, 16-33, 36-59 and 61 are neither anticipated by nor obvious over the art of record. Claims 1, 4-10, 12, 13, 16-33, 36-59 and 61 are now believed to be in condition for allowance.

Favorable action is earnestly solicited.

October 17, 2002

Respectfully submitted,



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File No. 5432/0I004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Ken LILJEGREN *et al.*

Serial No.: 09/730,380 Group Art Unit: 1625

Filed: December 5, 2000 Examiner: C. Aulakh

For: PHARMACEUTICAL COMPOSITION CONTAINING CITALOPRAM

CLAIMS PENDING AFTER ACCOMPANYING
RESPONSE UNDER 37 C.F.R. § 1.111

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

1. A tablet comprising crystals of a pharmaceutically acceptable salt of citalopram, wherein the median particle size of the crystals is at least 40 μm, which is prepared by direct compression of the pharmaceutically acceptable salt and pharmaceutically acceptable excipients.

4. The tablet according to claim 1 which does not contain a binder.

5. The tablet according to claim 1 which contains 2-60% w/w active ingredient calculated as citalopram base.

6. The tablet according to claim 1 which contains a filler selected from lactose, sugars, calcium phosphates, starch, modified starches, microcrystalline cellulose, calcium sulfate and calcium carbonate.

7. The tablet according to claim 6, wherein the filler is a microcrystalline cellulose.

8. The tablet according to claim 1 which contains a lubricant selected from metallic stearates, stearic acid, wax, hydrogenated vegetable oil, talc and colloidal silica.

9. The tablet according to claim 8, wherein the lubricant is magnesium stearate or calcium stearate.

10. The tablet according to claim 1 which is substantially free of lactose.

12. The tablet according to claim 1 wherein the pharmaceutically acceptable salt is citalopram hydrobromide or citalopram hydrochloride.

13. The tablet according to claim 12, wherein the pharmaceutically acceptable salt is citalopram hydrobromide.

16. Crystals of a pharmaceutically acceptable salt of citalopram wherein the median particle size of the crystals is at least 40μm.

17. Crystals according to claim 16, wherein the crystals are of citalopram

hydrobromide or citalopram hydrochloride.

18. Crystals according to claim 17, wherein the crystals are of citalopram hydrobromide.

19. Crystals according to claim 16, wherein the median particle size of the crystals is in the range of 40 - 200μm.

20. Method for manufacture of crystals of a pharmaceutically acceptable salt of citalopram having a median particle size of at least 40μm, said method comprising the steps of forming a solution of a pharmaceutically acceptable salt of citalopram in a solvent system at a first temperature, cooling the solution to a second temperature, seeding the solution by addition of crystals of said citalopram salt, followed by holding the solution at said second temperature and a controlled cooling the solution down to a third temperature, and isolating said crystals.

21. The method according to claim 20, wherein the median particle size of the crystals is in the range of 40 - 200μm.

22. The method according to claim 20, wherein the pharmaceutically acceptable salt of citalopram is citalopram hydrobromide or citalopram hydrochloride.

23. The method according to claim 22, wherein the pharmaceutically acceptable salt of citalopram is citalopram hydrobromide.

24. The method according to claim 20, wherein the solvent system comprises one or more alcohols and optionally water.

25. The method according to claim 24, wherein the solvent system is a mixture of methanol and water.

26. The method according to claim 25 wherein the methanol:water weight ratio is in the range of 5:1 to 50:1.

27. The method according to claim 20 wherein the solvent:solute weight ratio is in the range of 0.5:1 to 5:1.

28. The method according to claim 20 wherein said first temperature is in the range between 50°C and the refluxing temperature of the solvent system.

29. The method according to claim 20 wherein said second temperature is in the range of 20-40°C.

30. The method according to claim 20 wherein the step of holding the solution at said second temperature is from 30 minutes to 7 days.

31. The method according to claim 20 wherein said third temperature is in the range of 0-20°C.

32. The method according to claim 20 wherein said controlled cooling down is a gradual cooling down over a time span in the range of 5 minutes to 6 hours.

33. The method according to claim 20 wherein the step of isolating the crystals of a pharmaceutically acceptable salt of citalopram is performed by filtration.

36. The tablet of claim 1, which contains 10-40% w/w active ingredient calculated as citalopram base.

37. The tablet of claim 1, which contains 15-25% w/w active ingredient calculated as citalopram base.

38. The tablet of claim 6, wherein said filler is a sugar selected from the group consisting of sorbitol, mannitol, dextrose and sucrose.

39. The tablet of claim 6, wherein said filler is a calcium phosphate selected from the group consisting of dibasic, tribasic, hydrous and anhydrous calcium phosphate.

40. The tablet of claim 8, wherein said lubricant is a metallic stearate selected from the group consisting of magnesium, calcium and sodium stearate.

41. The tablet of claim 1, wherein the crystals have a median particle size of 40-200 μm.

42. The tablet of claim 1, wherein the crystals have a median particle size of 45-150μm.

43. The tablet of claim 1, wherein the crystals have a median particle size of 50-100μm.

44. Crystals according to claim 19, wherein the median particle size of the crystals is in the range of 45-150μm.

45. Crystals according to claim 19, wherein the median particle size of the crystals is in the range of 50-120μm.

46. The method according to claim 21, wherein the median particle size of the crystals in the range of 45-150μm.

47. The method according to claim 21, wherein the median particle size of the crystals in the range of 50-120μm.

48. The method according to claim 26, wherein the methanol:water weight ratio is in the range of 10:1 to 30:1.

49. The method according to claim 26, wherein the methanol:water weight ratio is in the range of 15:1 to 25:1.

50. The method according to claim 27, wherein the solvent:solute weight ratio is in the range of 0.7:1 to 2:1.

51. The method according to claim 27, wherein the solvent:solute weight ratio is in the range of 0.9:1 to 1.5:1.

52. The method according to claim 28, wherein said first temperature is in the range between 60°C and the refluxing temperature.

53. The method according to claim 28, wherein said first temperature is in the range between 64°C and the refluxing temperature.

54. The method according to claim 29, wherein said second temperature is in the range of 25-35°C.

55. The method according to claim 30, wherein the step of holding the solution at said second temperature is from 1 hour to 4 days.

56. The method according to claim 30, wherein the step of holding the solution at said second temperature is from 12 to 36 hours.

57. The method according to claim 32, wherein said time span is in the range of 15 minutes to 4 hours.

58. The method according to claim 32, wherein said time span is in the range of 30 minutes to 2 hours.

59. A method for manufacturing a citalopram dosage form, which comprises

providing a solution of a pharmaceutically acceptable salt of citalopram in a suitable solvent system at a first temperature;

cooling said solution to a second temperature below said first temperature;

seeding said solution with crystals of said citalopram salt;

holding said solution at said second temperature for a predetermined period of time;

cooling said solution to a third temperature that is lower than said second temperature to form citalopram crystals having a median particle size of at least 40μm;

isolating said crystals from said solution; and

directly compressing a predetermined quantity of crystals into a tablet.

61. The method of claim 59 which comprises compressing a pharmaceutically acceptable excipient with said crystals.

File No. 5432/0I004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Ken LILJEGREN *et al.*

Serial No.: 09/730,380 Group Art Unit: 1625

Filed: December 5, 2000 Examiner: C. Aulakh

For: PHARMACEUTICAL COMPOSITION CONTAINING CITALOPRAM

MARKUP ACCOMPANYING AMENDMENT UNDER 37 C.F.R. § 1.111

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

IN THE CLAIMS

Please amend claims 44 and 45 as follows.

44. Crystals according to claim 19, wherein the median particle size of the crystals is in the [rage] range of 45-150μm.

45. Crystals according to claim 19, wherein the median particle size of the crystals is in the [rage] range of 50-120μm.

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